Heart Rhythm Congress 2009
HRC2009
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Hilton Birmingham Metropole Hotel, Birmingham, UK
Education Technology Diversity

Cardiac Resynchronisation Therapy

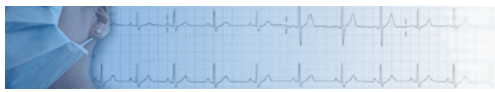
Evolving indications

Dr Tim Betts MD MBChB MRCP

Consultant Cardiologist & Electrophysiologist

Oxford Radcliffe Hospitals NHS Trust

Arrhythmia Alliance
The Heart Rhythm Charity
Promoting better understanding, diagnosis, treatment and quality of life for individuals with cardiac arrhythmias



Oxford Radcliffe Hospitals NHS
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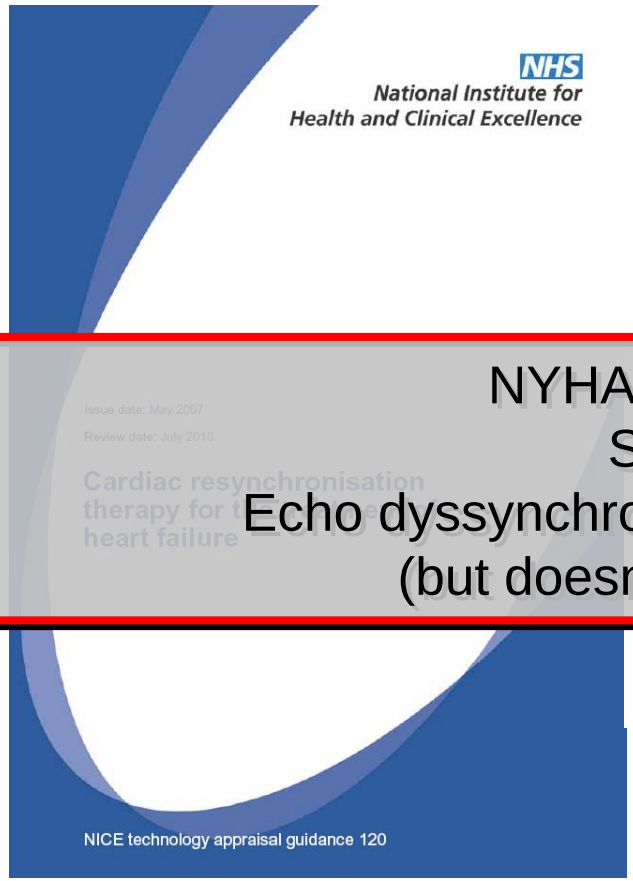
Heart Rhythm UK

Current CRT guidelines - UK



1.1 Cardiac resynchronisation therapy with a pacing device (CRT-P) is recommended as a treatment option for people with heart failure who fulfil all the following criteria.

- They are currently experiencing or have recently experienced New York Heart Association (NYHA) class III–IV symptoms.
- They have a QRS duration of 150 ms or longer estimated by ECG and
- or with a QRS duration of 120–149 ms estimated by ECG and mechanical dyssynchrony that is confirmed by echocardiography.
- They have a left ventricular ejection fraction of 35% or less.
- They are receiving optimal pharmacological therapy.

NYHA III or IV, LVEF ≤35%
Sinus rhythm only
Echo dyssynchrony required if QRS 120-150 ms
(but doesn't say which parameters)

Current CRT guidelines - Europe

Europace (2007) 9, 959–998
doi:10.1093/europace/eum189

ESC Guidelines

Guidelines for cardiac pacing and cardiac resynchronization therapy

The Task Force for Cardiac Pacing and Cardiac Resynchronization Therapy of the European Society of Cardiology. Developed in Collaboration with the European Heart Rhythm Association

Online publish-ahead-of-print 28 August 2007

Authors/ Task Force Members: Panos E. Vardas* (Chairperson) (Greece); Angelo Auricchio (Switzerland); Jean-Jacques Blanc (France); Jean-Claude Daubert (France); Helmut Drexler (Germany); Hugo Ector (Belgium); Maurizio Gasparini (Italy); Cecilia Linde (Sweden); Francisco Bello Morgado (Portugal); Ali Oto (Turkey); Richard Sutton (UK); Maria Trusz-Gluza (Poland)

NYHA III or IV, LVEF ≤35%
Sinus rhythm (unless undergoing ablate and pace or brady pacing)
QRS ≥120ms – no echo dyssynchrony required
LV dilatation

classes III–IV despite OPT, with LVEF ≤ 35%, LV dilatation [LV dilatation/different criteria have been used to define LV dilatation in controlled studies on CRT: LV end-diastolic diameter >55 mm; LV end-diastolic diameter >30 mm/m^2, LV end-diastolic diameter >30 mm/m (height)], normal sinus rhythm and wide QRS complex (≥120 ms).

3.2.2. Recommendations for the use of biventricular pacing in heart failure patients with a concomitant indication for permanent pacing

Heart failure patients with NYHA classes III–IV symptoms, low LVEF ≤ 35%, LV dilatation and a concomitant indication for permanent pacing (first implant or upgrading of conventional pacemaker). Class IIa: level of evidence C.[289,313]

3.2.3 Recommendations for the use of an implantable cardioverter defibrillator combined with biventricular pacemaker (CRT-D) in heart failure patients with an

pacing in heart failure patients with permanent atrial fibrillation

Heart failure patients who remain symptomatic in NYHA classes III–IV despite OPT, with low LVEF ≤ 35%, LV dilatation, permanent AF and indication for AV junction ablation. Class IIa: level of evidence C.[311,312]

Current CRT guidelines – USA

ACC/AHA/HRS 2008 Guidelines for Device-Based Therapy of Cardiac Rhythm Abnormalities: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices) Developed in Collaboration With the American Association for Thoracic Surgery and Society of Thoracic Surgeons

Andrew E. Epstein, John P. DiMarco, Kenneth A. Ellenbogen, N.A. Mark Estes, III, Roger A. Freedman, Leonard S. Gettes, A. Marc Gillinov, Gabriel Gregoratos, Stephen C. Hammill, David L. Hayes, Mark A. Hlatky, L. Kristin Newby, Richard L. Page, Mark H. Schoenfeld, Michael J. Silka, Lynne Warner Stevenson, and Michael O. Sweeney

J. Am. Coll. Cardiol. 2008;51;e1-e62; originally published online May 15, 2008; doi:10.1016/j.jacc.2008.02.032

CLASS I

1. **For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and sinus rhythm, CRT with or without an ICD is indicated for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms with optimal recommended medical therapy. *(Level of Evidence: A)*** (222,224,225,231)

CLASS IIa

1. **For patients who have LVEF less than or equal to 35%, a QRS duration greater than or equal to 0.12 seconds, and AF, CRT with or without an ICD is reasonable for the treatment of NYHA functional Class III or ambulatory Class IV heart failure symptoms on optimal recommended medical therapy. *(Level of Evidence: B)*** (220,231)

LVEF ≤35%

NYHA III or ambulatory IV (or I or II if bradycardia pacing indication)

Sinus rhythm or AFib

QRS ≥120ms – no echo dyssynchrony required

CLASS IIb

1. **For patients with LVEF less than or equal to 35% with NYHA functional Class I or II symptoms who are receiving optimal recommended medical therapy and who are undergoing implantation of a permanent pacemaker and/or ICD with anticipated frequent ventricular pacing, CRT may be considered. *(Level of Evidence: C)*** (231)

Why move beyond the guidelines?

- Only a small proportion of heart failure patients are identified as eligible for CRT
- Still at best have a 25-30% failure to respond. As disease progresses the chance to modify it may be missed
- "**Prevention is better than cure**": Address the problem while the disease process is still modifiable / reversible, i.e. before symptoms develop, before QRS gets too wide or before LV function deteriorates too much

Evolving indications

- Atrial fibrillation
- Device upgrades from pacing-induced wide QRS insetting of NYHA III and LVEF <35%

- NYHA I or II patients with wide QRS and LVEF<35%
- Narrow QRS with NYHA III or IV and LVEF<35%
- Brady indication (with narrow QRS and/or NYHA 1 or 2)
- Preserved LV function (heart failure symptoms or brady pacing with no symptoms/LV impairment)

- Congenital heart disease
- Arrhythmia prevention
- Post CPB

Atrial fibrillation

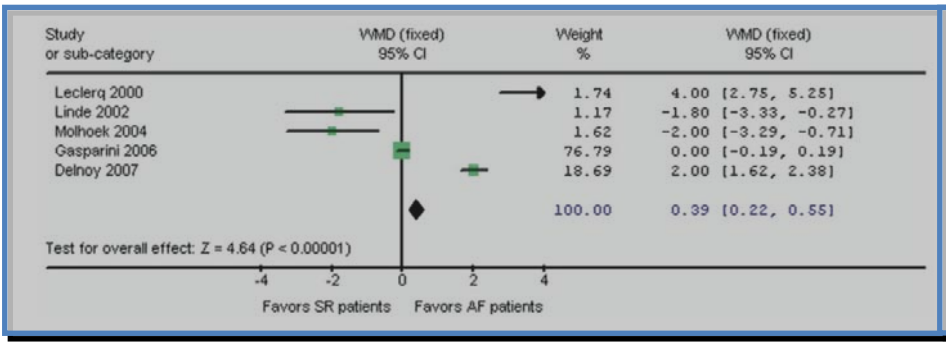
- Majority of CRT trials excluded patients with permanent Afib
- AV synchrony cannot be achieved
- Rapidly-conducted AFib may reduce % of BiV pacing
- Base rate may be programmed higher, affecting diastolic filling

- 30% NYHA III and IV patients have Afib
- 100% BiV pacing can be achieved with AVJ ablation if necessary
- Physicians are implanting in Afib patients regardless of the guidelines (23% in EuroCRT survey)

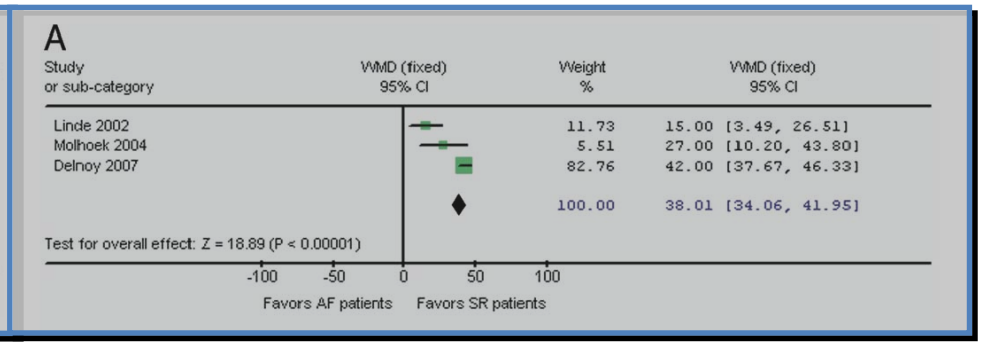
Atrial fibrillation
Wide QRS, NYHA 3 and LVEF<35%

- CARE-HF
  - New onset atrial fibrillation post-CRT implant did not diminish the beneficial effects

- Metaanalysis (Upadhyay GA, *JACC,* 2008)
  - 1164 pts from 5 prospective cohort studies. 367 AF, 797 SR
  - Similar mortality and NYHA benefit.
  - SR greater 6MWT improvement, AF greater LVEF improvement



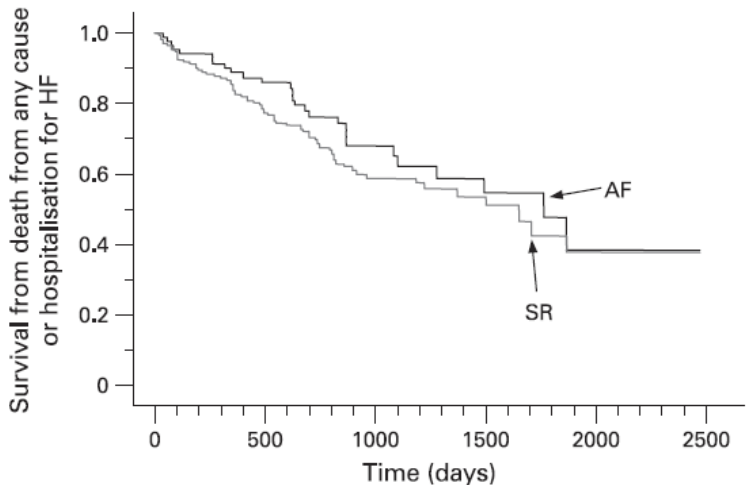
NYHA status



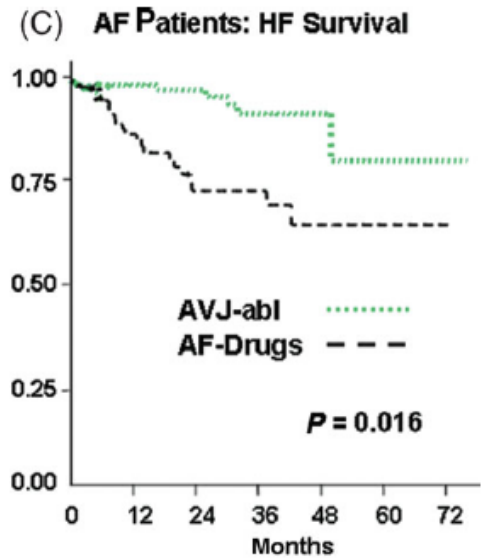
6 minute walk distance

Atrial fibrillation
Wide QRS, NYHA 3 and LVEF<35%

- Khadjooi K, *Heart*, 2008
  - 300 pts, 66 chronic AFib. Over long term followup Afib patients had a similar degree of benefit (mortality, functional and echo parameters) to SR patients

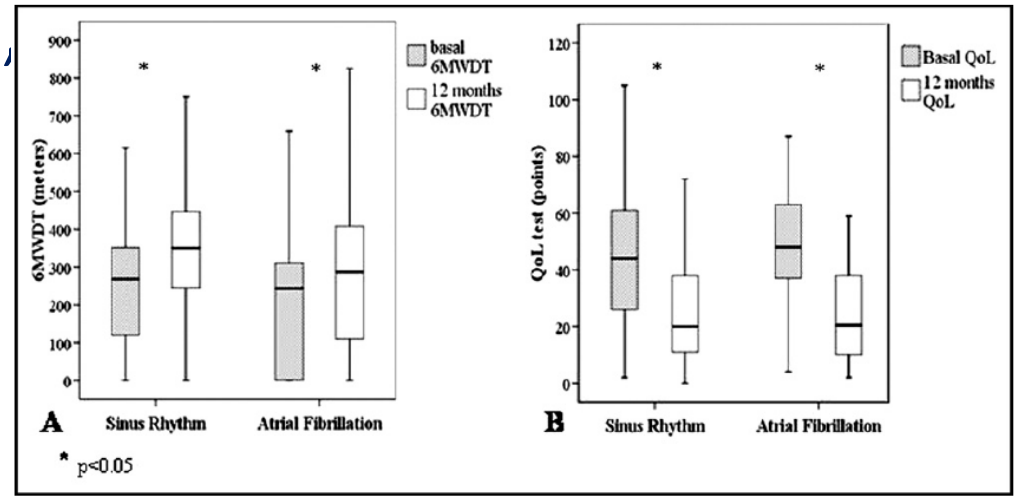


- Gasparini M, *Eur Heart J*, 2008
  - 243 pts with Afib – 118 had AVJ abl
  - Mortality benefit is in those with AVJ ablation



Atrial fibrillation
Wide QRS, NYHA 3 and LVEF<35%

- SPARE study (Tolosana, *AJC*, 2008)
  - 126 pts with Afib
  - Similar response to SR pts
  - Higher mortality in Afib group
  - Only 15% required AVJ abl

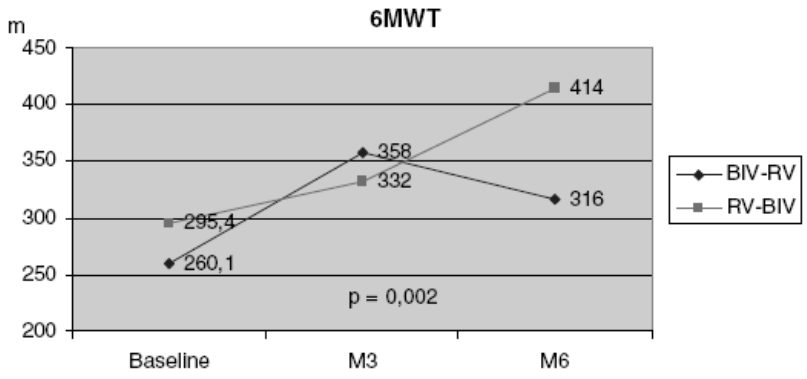


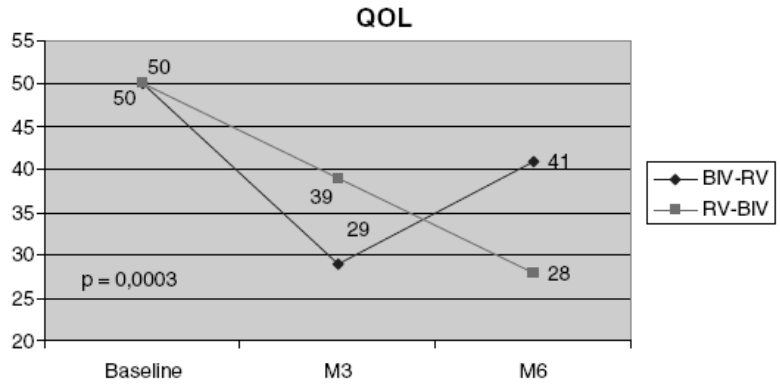
6MWD QOL

Ongoing trial: **AVERT-AF** is testing the hypothesis that AVJ ablation followed by biventricular pacing significantly improves exercise capacity and functional status compared to pharmacologic rate control in patients with chronic AF, an indication for ICD and depressed ejection fraction, regardless of rate or QRS duration.

Upgrading from single site pacing
Pacing-induced wide QRS, NYHA 3 or 4 and LVEF<35%

- LeClercq C, *PACE*, 2007
  - Pts with RV pacing, NYHA III and poor LV coming for PPM upgrade
  - Crossover after 3 months



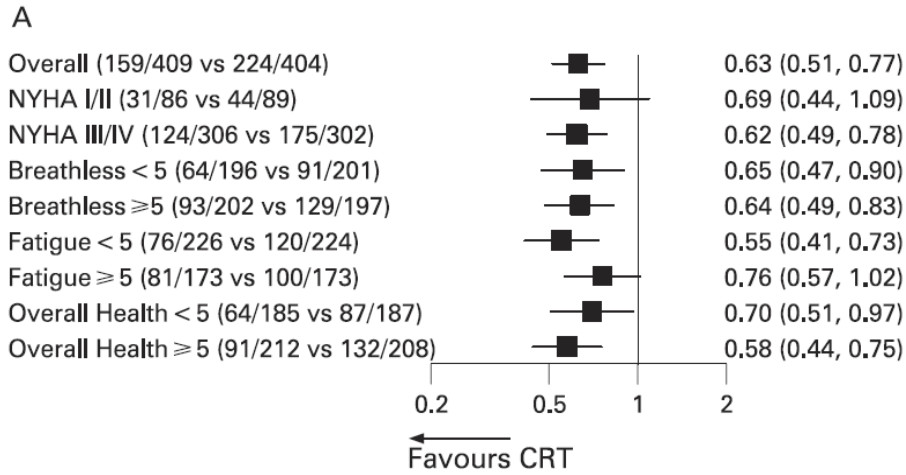


EuroCRT survey

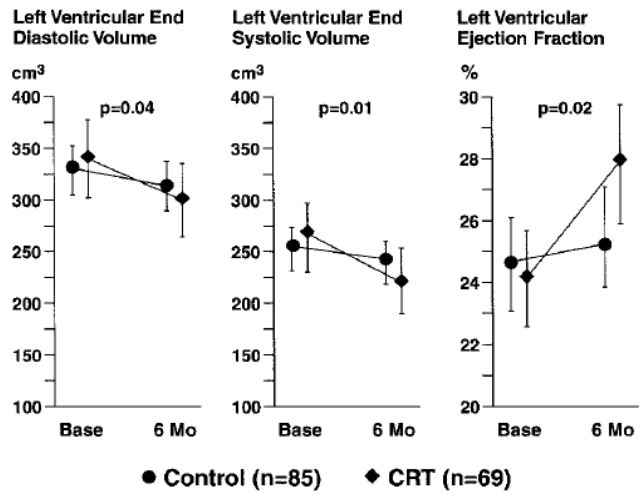
26% patients already had a device in

NYHA class I and II
Wide QRS, severely impaired LVEF

- Can be hard to distinguish NYHA II from III. NYHA status can fluctuate over time
- In **CARE-HF** only 2/3 patients agreed with their physicians NYHA assessment – 21.5% felt themselves to be NYHA I or II
- **MIRACLE InSync ICD II study**
  - NYHA class II patients had no functional benefit but did show a reduction in LV volumes



CARE-HF primary endpoint



MIRACLE InSync ICD II

NYHA class I and II
Wide QRS, severely impaired LVEF

MADIT-CRT (Sinus rhythm, LVEF<30%, QRS>130ms, NYHA I or II)

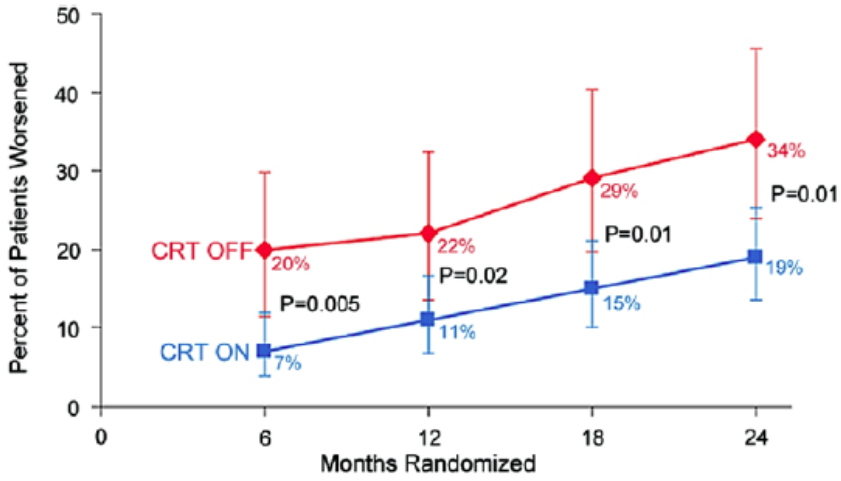
- ARR of HF events at 3 year follow-up was 29%-20% = **9% (NNT 12)**

- For every 1000 patients who are prescribed a CRT-ICD rather than an ICD, after 2.4 years:
    - 75 will have unsuccessful procedures and not get a LV lead
    - An additional 40 will need their LV leads repositioning in the first month
    - Over the next 3 years no additional lives will be saved (75 patients will die)
    - Over the next 3 years 90 patients will be prevented from having a heart failure admission or home treatment with iv diuretics
    - Despite having CRT, 200 patients will still have a heart failure admission or home treatment with diuretics

NYHA class I and II
Wide QRS, severely impaired LVEF

REVERSE (Sinus rhythm, NYHA I or II, LVEF<40%, QRS>120ms, LVEDD >55mm)

- Clinical composite of mortality, crossover to CRT or worsening heart failure. Worsened, unchanged or improved. Echo measurements (LEVSVi) secondary endpoint.
- 96% successful implant rate
- 34% worsened in CRT-off group vs 19% in CRT-on group
- 10% reduction in HF hospitalizations by 2 years
- QRS >150ms tended to derive more benefit



NYHA class I and II
Wide QRS, severely impaired LVEF

- Ongoing trial: RAFT (Resynchronization/Defibrillation for Ambulatory Heart Failure Trial)
    - ICD indication, LVEF<30%, NYHA II, QRS>120ms (or paced >200). Mortality + HF hospitalisation. SR or AF with controlled V rate

May need time to show benefit in minimally-symptomatic patients

Functional assessment is less relevant in this group

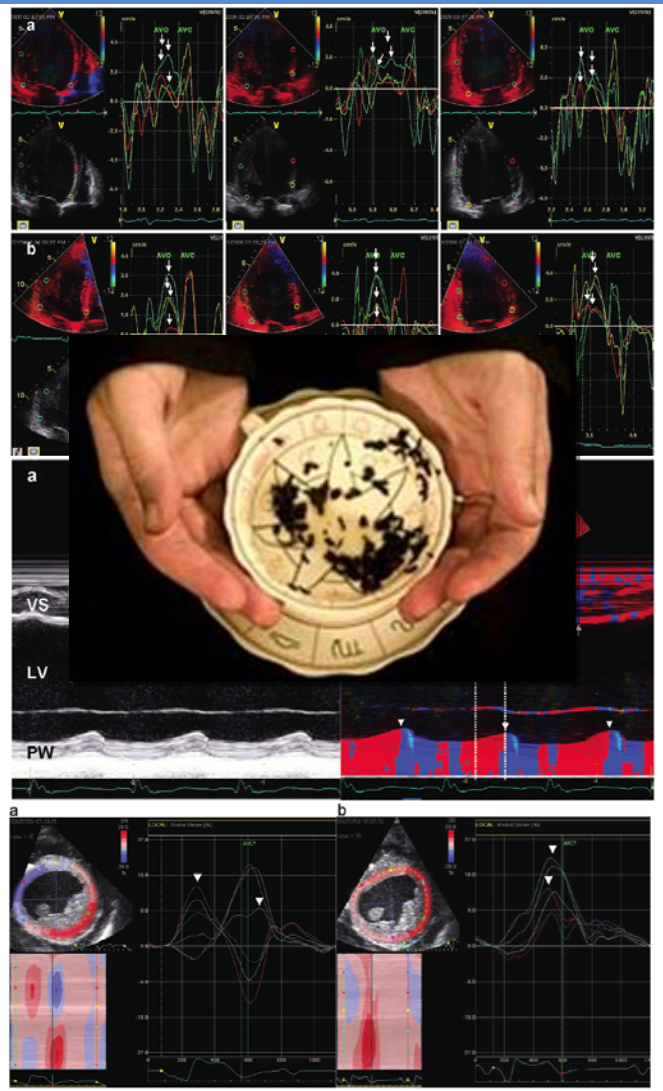
Echo (mechanical) *vs* ECG (electrical) dyssynchrony

- 48% of CRT candidates with QRS 120-150 ms and 28% with QRS >150ms don't have mechanical dyssynchrony

- 2/3 of NYHA III or IV patients with LVEF<35% don't have wide QRS complexes
- 30% of these have mechanical dyssynchrony on echo

Echo (mechanical) *vs* ECG (electrical) dyssynchrony

- PROSPECT study
  - Assessed single echo parameters ability to predict response
  - Unable to predict response above the 60-70% rate of the ECG
  - Unacceptable variability between operators



Narrow QRS
NYHA 3 or 4, LVEF<35%

- Achilli, *JACC*, 2003
  - Incomplete LBBB (<120) seemed to benefit as much as QRS>120 ms
- Gasparini, *PACE*, 2007:
  - 12% of a cohort of 376 pts had QRS <120 ms (not selected by echo dyssynchrony)
  - Gradual improvement in LV measurements in both groups over 3 years – narrow increasing more rapidly in first year. Both groups had functional improvement
- Yu, *JACC*, 2006
  - Narrow QRS with TDI dyssynchrony benefitted as much as wide QRS
  - The more dyssynchrony, the greater the remodelling. Functional benefit too.
  - No control group (? placebo effect)
- Jeevanantham, *Cardiology Journal*, 2008 Meta-analysis
  - 3 trials with only 98 patients
  - narrow QRS benefit (LVEF, 6MWT and NYHA).

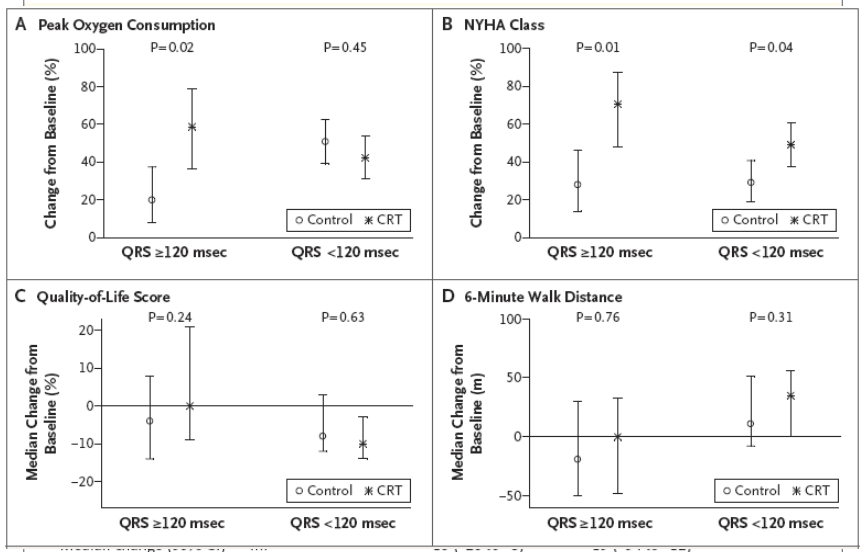
Narrow QRS
NYHA 3 or 4, LVEF<35%

RethinQ study

- ICD indication, NYHA III, QRS<**130ms**, LVEF<35%, 2 out of 3 mechanical dyssynchrony criteria
- Overall, no benefit in
  - Primary endpoint of VO2 max (improvement in 46% on vs 41% off)
  - Secondary endpoints of QOL or 6MWT
  - Echo measurements
- Improvement in
  - Secondary endpoint of NYHA status (59% vs 29%).
- The **120-130ms** subgroup did improve in VO2 max and NYHA class, but not QOL and 6MWT.
- DCMs with CRT improved NYHA and 6MWT but no difference in QOL or VO2 max

Table 2. Effect of Cardiac Resynchronization on Primary and Secondary End Points and Other Measures.*

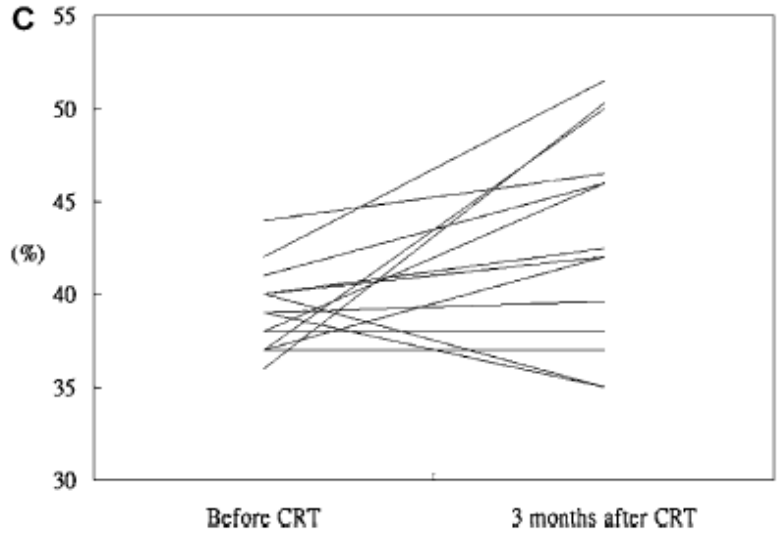
Variable	Control Group	CRT Group	P Value
Primary end point			
Change in peak oxygen consumption			0.63
No. of patients	80	76	
Median change (95% CI) — ml/kg/min	0.5 (−0.3 to 1.1)	0.4 (-0.6 to 1.2)	
Increase of ≥1.0 ml/kg/min — no. (%)	33 (41)	35 (46)	
Secondary end points			
Change in quality-of-life score†			0.91



Change in end-diastolic diameter			0.49
No. of patients	77	72	
Median change (95% CI) — mm	−1 (−2 to 1)	0 (−2 to 0)	
Change in end-systolic diameter			0.34
No. of patients	77	72	
Median change (95% CI) — mm	0 (−2 to 2)	−1 (−3 to 0)	
Change in degree of mitral regurgitation — no. (%)			>0.99
No. of patients	80	76	
Improved by 1 or more grade	9 (12)	8 (11)	
No change	61 (80)	60 (81)	
Worsened by 1 or more grade	6 (8)	6 (8)	

LVEF>35%
Wide QRS, NYHA III or IV

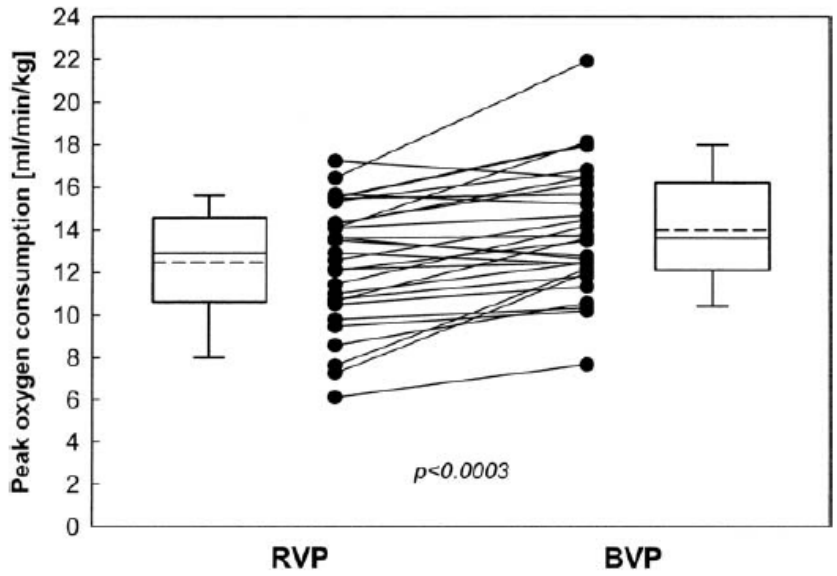
- Fung J, *JCE*, 2006
  - 15 patients LVEF 35-45% followed for 3 months
  - Benefit in echo markers (eg. LVEF improved from 39.1±2.2 to 44.2±5.5%) and NYHA status but not 6MWT or QOL
  - Changes comparable with matched conventional LVEF<35% pts (apart form QOL)



Changes in LVEF

Bradycardia pacing indication
LVEF <40%

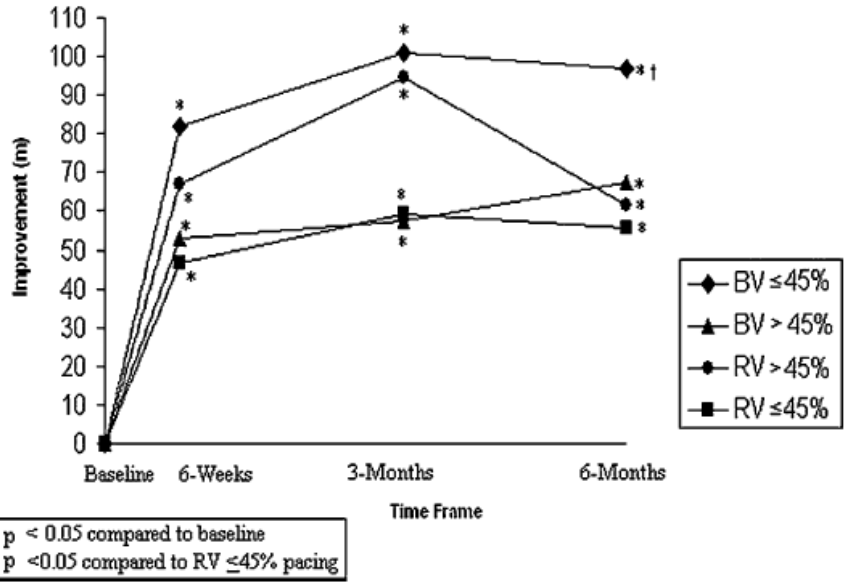
- HOBIPACE
  - LVEF<40%
  - Mainly NYHA III
  - Most wide QRS before pacing
  - 2/3 in SR
  - BiV resulted in
    - reduced LV volumes
    - increased LVEF
    - increased functional class and VO2 max

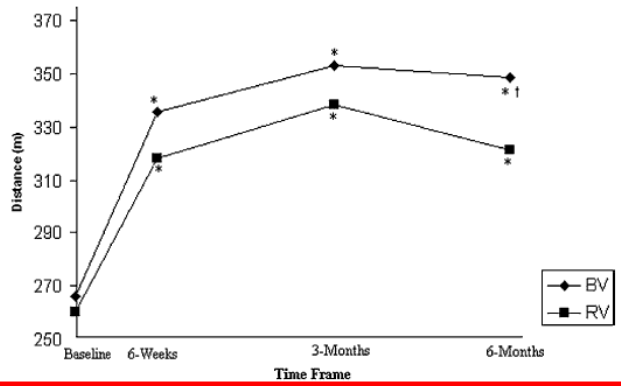


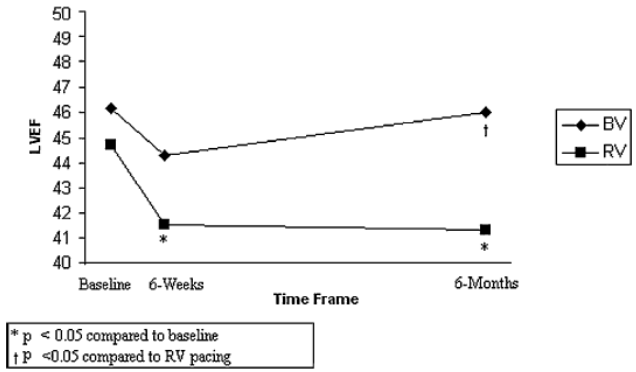
Bradycardia pacing indication
AVJ ablation

PAVE (*JCE*, 2005)

- Patients undergoing AVJ abl and PPM implant
- BiV patients had a greater 6 month improvement in 6MWT and LVEF





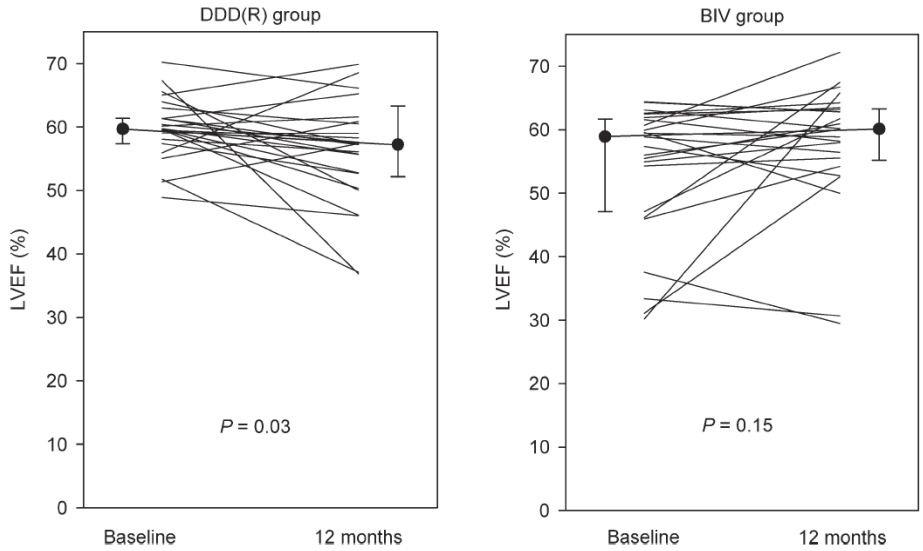


Differences due to late deterioration in RV LVEF>45% and NYHA I patients

Bradycardia pacing indication

Albertson, *Europace* 2008

- 50 pts with CHB randomised to DDD(R) or BiV device
- With 12 month FU, BNP decreased in BiV but was unchanged in DDDR (but was higher in beginning in BiV group who had significantly wider QRS complexes).
- Slight decrease in LVEF in DDD(R) group.



Bradycardia pacing indication
Ongoing studies

- BioPACE study: Does CRT offer a clinical benefit in patients with conventional indications for permanent ventricular pacing, regardless of spontaneous QRS duration and morphology or LV size and function?
- PREVENT-HF: Standard bradycardia indication (>85% V pacing expected) and NYHA 1 or 2. RV vs BiV. Endpoint is change in LVEDD
- PACE (Pacing to Avoid Cardiac Enlargement): LVEF>45%, DDD(R) vs BiV. Functional, echo and endocrine assessment

Congenital heart disease

- Majority of patients reported in series have involved upgrades from single site pacing
- In the 2 largest, >100 pt series, most patients were NYHA II
- Majority had systemic LV, a smaller proportion systemic RV and very few single functional ventricle
- 59% involved surgical epicardial leads
- Response rates are very high (>85%)
- Requires individualisation and novel approaches

Reduction in ventricular arrhythmia burden

- CONTAK-CD
  - No difference between ICD (16%) and CRT-D (15%) arms in ventricular arrhythmia events
- Insync III Marquis
  - CRT responders (reduction in LV volumes) had a reduction in VPBs and treated VT/VF episodes
- Insync ICD Italian Registry
  - Responders (defined by reduction in LV dimensions) had a greater reduction in arrhythmia burden
- Lin, Heart 2008
  - Upgrading a standard ICD to CRT-D does not reduce frequency of ventricular arrhythmias

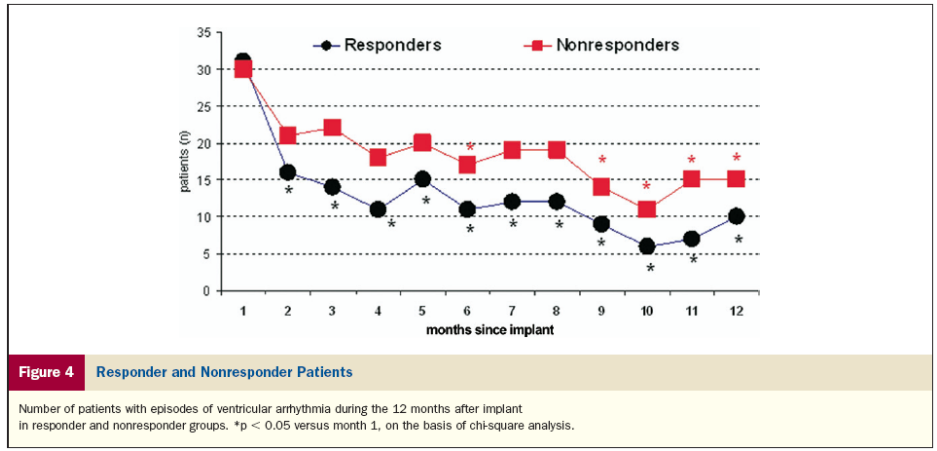
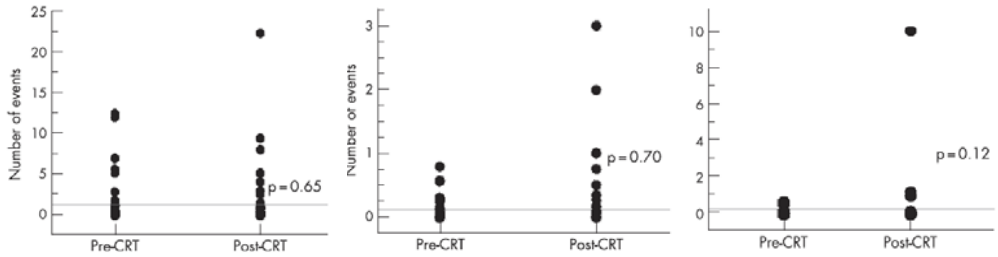


Figure 4 Responder and Nonresponder Patients

Number of patients with episodes of ventricular arrhythmia during the 12 months after implant in responder and nonresponder groups. *p < 0.05 versus month 1, on the basis of chi-square analysis.



Non-sust VT Sust VT/VF VF

Post CPB

- Flynn, *EurJCS* 2005
  - Acute haemodynamics are better with LV than RV single site AV sequential pacing
- Muehlschlegel, *J Card Surg* 2007
  - Acute haemodynamic benefit immediately after coming off bypass with BiV vs DDD single site
- Evonich, *JTCS* 2008
  - Poor LV, narrow QRS. BiV pacing help a few in the first 12 hours post surgery but actually decreased CO in a greater proportion
- Eberhardt , *JTCS* 2009
  - No benefit with temp BiV pacing in pts with narrow QRS and LVEF <40% post CABG

Why “evolve” beyond the guidelines?

- In a hospital discharge cohort 3% of patients with ischaemic or dilated cardiomyopathy are eligible (LVEF <0.35, QRS >120 ms, sinus rhythm, and NYHA class III or IV symptoms despite OPT). This drops to 1% if symptoms despite spironolactone is a criteria

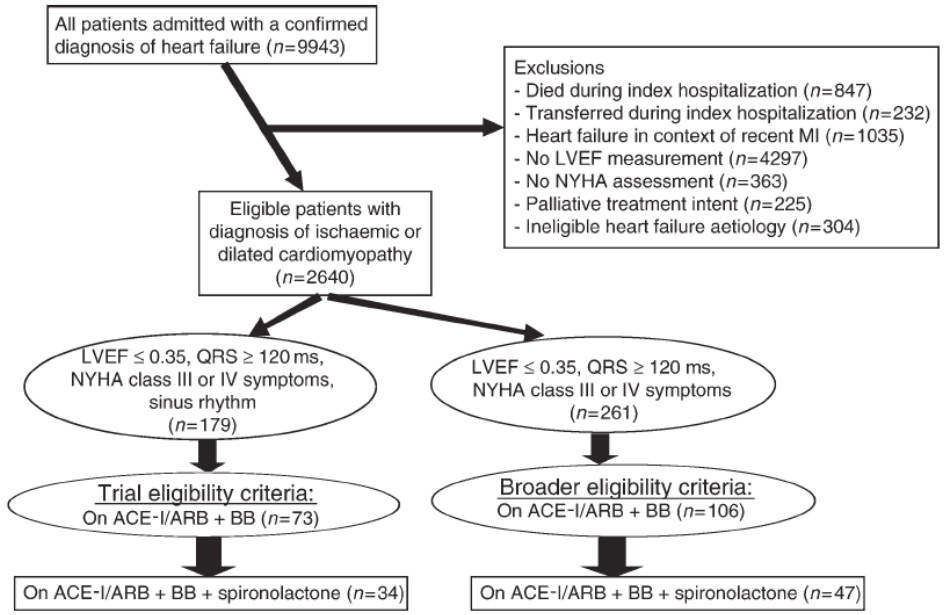


Figure 1 Proportion eligible for CRT in hospital discharge cohort.

McAlister FA, *EHJ,* 2006

Why “evolve” beyond the guidelines?

- In a specialty clinic cohort, 21% of patients with ischaemic or dilated cardiomyopathy are eligible. This drops to 18% if symptoms despite spironolactone is a criteria.

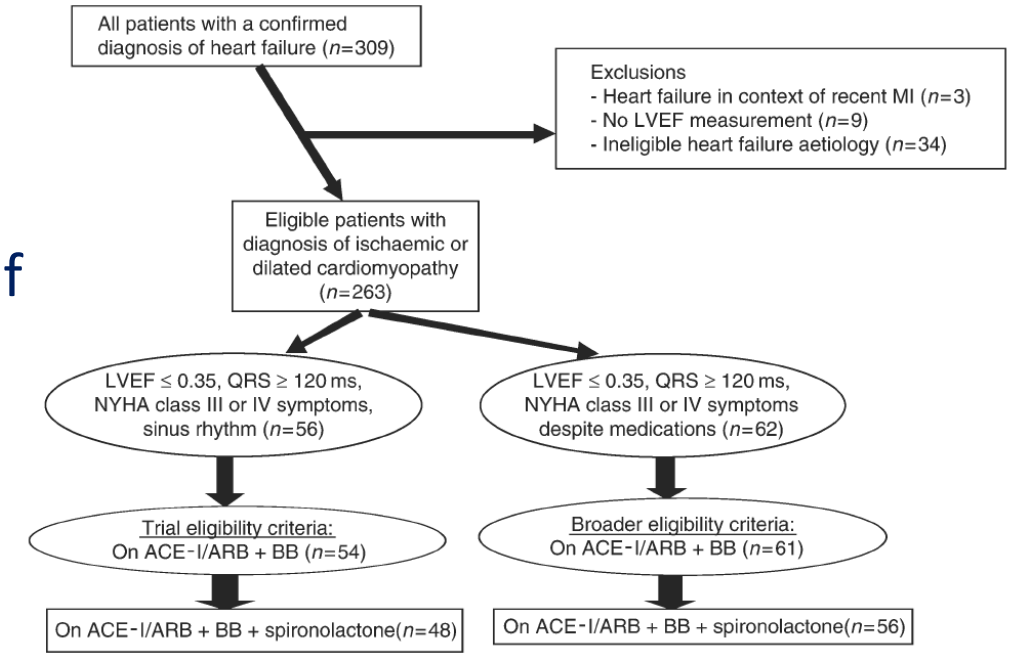


Figure 2 Proportion eligible for CRT in specialty clinic cohort.

McAlister FA, *EHJ,* 2006

Summary: Which direction to evolve towards in 2008

- Atrial fibrillation
  - Benefit just as much as sinus rhythm patients, but consider AVJ ablation to guarantee 100% BiV pacing
- Upgrading of RV paced NYHA III, LVEF<35% patients
- Prophylactic BiV pacing for bradycardia indications in LVEF<35%
- NYHA class II
  - Reduced hospitalizations, beneficial remodelling
  - QRS>150ms may benefit more
  - But …… why not just upgrade when symptoms develop?

Evolution or “guideline creep”

- EuroCRT survey (Bogale N. European Society of Cardiology 2009 Congress; August 30-September 2, 2009: Barcelona, Spain)
    - 26% already have a device in (upgrade)
    - 23% have AFib
    - 9% QRS<120 ms, 10% QRS 120-130 ms
    - 2% NYHA I, 20% NYHA II
    - 17% LVEF>35%

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Cardiac Resynchronisation Therapy
Evolving indications

Dr Tim Betts MD MBChB MRCP
Consultant Cardiologist & Electrophysiologist
Oxford Radcliffe Hospitals NHS Trust